Secondary Lymphoid Malignancy in Two Children With Neuroblastoma

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Secondary lymphoid malignancy, particularly acute lymphoblastic leukemia (ALL), is rare. We report one case of ALL and another case of mediastinal lymphoblastic lymphoma developed after treatment for neuroblastoma. The secondary ALL characterized by short latency period and an 11q23 translocation apparently was induced by etoposide treatment. The pathogenesis of the secondary lymphoma is less certain and may be related to previous treatment with cyclophosphamide and radiotherapy, host susceptibility, or chance occurrence. One child died of progressive lymphoma and the other remains in remission 1 year following allogeneic bone marrow transplantation. Additional studies are needed to determine the risk, pathogenesis, and optimal treatment for secondary lymphoid malignancy.

Key words: secondary malignancy, neuroblastoma, acute lymphocytic leukemia, 11q23 abnormality

INTRODUCTION

Secondary leukemia is a well-recognized late complication of antineoplastic therapy and typically manifests as acute myeloid leukemia (AML) [1,2]. Acute lymphoblastic leukemia (ALL) represented only 5 to 10% of secondary leukemias in one recent review [3]. Unlike secondary AMLs which are clearly induced by antineoplastic therapy (e.g., alkylating agents and topoisomerase II inhibitors) in most instances, the pathogenesis and retrieval therapy for secondary ALL are less well-defined, although the development of secondary ALL has also been demonstrated to be related to DNA topoisomerase II inhibitors [2,3]. Here, we describe two children with neuroblastoma who subsequently developed lymphoid malignancy in an attempt to address these issues.

Case Reports

Case 1. This 12.7-year-old boy presented in October 1982 with fever, cough, and dyspnea. At presentation, his leukocyte count was 2×10^9/L with normal differential, hemoglobin 9.5 g/dL, platelet count 269×10^9/L, serum lactate dehydrogenase level 810 IU/L, IgG 920 mg/dL, IgA 230 mg/dL, and IgM 304 mg/dL. He had no hepatosplenomegaly but chest x-ray and CT scan revealed a mediastinal mass without pleural fluid effusion. Biopsy of the enlarged supraclavicular lymph nodes disclosed lymphoblastic lymphoma of T-cell immunophenotype (E-rosette positive). Bone marrow examination showed the presence of 20% lymphoblasts. He was treated with intensive combination chemotherapy with adriamycin/vincristine/cyclophosphamide/prednisone, prednisone/vincristine/L-asparaginase, and teniposide/cytarabine, as well as intrathecal methotrexate. He developed a mediastinal recurrence 9 months later, which was unresponsive to 49.5 Gy local irradiation and retrieval chemotherapy. He died of progressive disease in January 1984.

Pertinent past history revealed that the child was diagnosed to have neuroblastoma (left adrenal primary, stage I/II) in December 1970, at the age of 10 months. He underwent tumor resection followed by 18-Gy irradiation to the tumor bed and combination therapy with vincristine and cyclophosphamide for 2 years. He also had two episodes of nephrotic syndrome, one diagnosed in 1974 and the other in 1979. There was no history of familial predisposition to cancer.

Case 2. This 26-month-old boy was diagnosed to have stage IV neuroblastoma in December 1991, at the age of 3 months. At that time, he had huge hepatosplenomegaly, a calcified tumor at the right adrenal gland

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with enlarged adjacent and para-aortic lymph nodes, and metastatic tumor clumps in the bone marrow. He had elevated urinary concentrations of VMA (728 μg/mg of creatinine) and HVA (363 μg/mg of creatinine) as well as an increased serum neuron-specific enolase (75 ng/ml), but no evidence of N-myc amplification in the tumor sample biopsied from the liver. He was treated with vincristine/cyclophosphamide and vincristine/adriamycin combinations; due to poor initial response, etoposide/cisplatin was added. He completed all treatment in January 1993 with cumulative doses of etoposide 2,700 mg/m^2 and doxorubicin 340 mg/m^2.

In October 1993, during a routine follow-up visit, he was found to be febrile and pale. Leukocyte count was 2.9×10^9/L, hemoglobin 6.1 g/dL, and platelet count 29×10^9/L. Bone marrow examination disclosed 49.5% replacement by lymphoblasts with a high N/C ratio and negative myeloperoxidase reactivity (FAB L1-type). Immunophenotype was consistent with B-precursor ALL—positive for CD19 and HLA-DR; and negative for CD10, CD34, and myeloid-associated antigens (CD13 and CD33). The karyotype of the leukemic cells was 46,XY,t(5;11)(q35;q23) and rearrangement of MLL gene was demonstrated.

The child was treated with combination chemotherapy consisting of adriamycin/vincristine/cyclophosphamide, prednisone/vincristine/L-asparaginase, and triple intrathecal therapy. He underwent allogeneic bone marrow transplantation in June 1994 during complete remission with an HLA-matched sibling donor. Conditioning regimen consisted of triple intrathecal therapy (days −14 and −9), 6-Gy irradiation in three fractions to the brain (on days −13, −12), total body irradiation 12 Gy in six fractions (on days −8 to −5), and cyclophosphamide 60 mg/kg/dose for two doses (on days −3 and −2). A total of 4.4×10^8/kg of donor cells were infused. Methotrexate and cyclosporin were given for prophylaxis against graft-vs.-host disease. Except for a grade I acute graft-vs.-host disease involving skin, the child has remained well in remission since the transplantation.

DISCUSSION

As the cure rate for childhood malignancies increases, so does the number of patients at risk for development of second malignancies. The risk of second cancer varies according to the primary malignancy, reflecting the patients' underlying immune function, the curability of the first cancer, and more importantly, the type of primary antineoplastic therapy. Smith et al. [4] reviewed the records of 162 patients who had developed a second malignancy after treatment for childhood cancer over a 40-year time period. The most common primary malignancy was Hodgkin's disease (n = 33) followed by soft tissue sarcoma (n = 28); neuroblastomas was found in only five cases. The second malignancy of these five neuroblastoma cases were bone sarcoma and thyroid carcinoma; none had secondary leukemia. By contrast, in a recent registry for second malignancy by the Pediatric Oncology Group in Japan, an additional six patients with neuroblastoma developed AML/myelodysplasia (n = 5) or ALL (n = 1) as secondary neoplasm (unpublished observation). Likewise, both of our cases had lymph-hematopoietic malignancy as their second cancer. The eight cases including our two were from approximately 2,700 neuroblastoma cases over the past 23 years; however, six of them, especially all five AML/myelodysplasia cases developed during 1987–1993. Conceivably, the recent apparent increase in hematopoietic malignancy in patients with neuroblastoma reflects the use of intensive chemotherapy in contemporary protocols.

The more frequent use of epipodophyllotoxins undoubtedly leads to the increase of secondary AML in patients with neuroblastoma. Indeed, all patients with secondary AML/myelodysplasia from the registry in Japan had received epipodophyllotoxins. The pathogenesis of the development of secondary lymphoid malignancy in patients with neuroblastoma is less certain. In a recent review of secondary ALL by Hunger et al. [3] two of three patients with neuroblastoma had received epipodophyllotoxins. Importantly, one of the two patients tested had the t(4;11)(q21;q23) chromosomal abnormality. Pui et al. [5] identified three cases of secondary ALL with the t(4;11) who had received epipodophyllotoxins for their primary malignancy. Secker-Walker et al. [6] also reported a similar case. In this study, the secondary ALL in case 2 is likely induced by the etoposide treatment, although the patient also received 340 mg/m^2 of doxorubicin, another DNA topoisomerase II inhibitor, and the contribution of combined dose intensive treatment must be considered. The presence of 11q23 chromosomal abnormality in association with MLL gene rearrangement and short latency period (2 years and 2 months) are all compatible with epipodophyllotoxin-induced leukemia [7,8].

The cause of secondary T-lymphoma in our case 1 is less certain. Although it may relate to previous treatment with radiotherapy and alkylation, the development of secondary ALL in this patient could also represent host susceptibility or a chance occurrence. In this regard, two cases with secondary ALL reported by Pratt and Pui [9] did not receive chemotherapy or radiotherapy. Unfortunately, no lymphoma cells were available to be characterized at the cytogenetic and/or molecular level with current techniques to further pursue the pathogenesis in this case.

The prognosis of secondary ALL appears to be dismal [3,4,5,9–12]. Virtually all of the reported cases died of leukemia or complications from the retrieval chemotherapy. In this study, one child treated with allogeneic bone

marrow transplant remain in remission 1 year after the procedure. Additional studies are needed to determine the efficacy of bone marrow transplantation in these patients.

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